C. Remarks/Argument

Reconsideration of this application is respectfully requested. Upon entry of the amendments, claims 1-9 and 13 will be pending. Claims 10-12 and 14-48 have been canceled herein without prejudice or disclaimer to being pursued in a later filed application. Claims 1-3, 8, 9, and 13 have been amended herein for clarity and to more particularly point out and distinctly claim the invention. Support for these amendments can be found throughout the application and claims as filed. Thus, no new matter has been added.

Enablement

The sole rejection in this application is not based on the prior art. Rather, claims 1-13 were rejected under 35 U.S.C. § 112, ¶ 1 for lack of enablement. The Examiner alleges that in view of the *Wands* factors, the specification fails to teach one of ordinary skill in the art how to make and/or use the invention recited by claims 1-13 without undue experimentation. *See* Office Action at pages 4-11. Without acquiescing to the rejection, claims 10-12 are canceled herein. Thus, the rejection is moot with respect to these claims. Applicants traverse the rejection as it may apply to the remaining claims as amended.

Independent claim 1, from which claims 2-9 depend either directly or indirectly, now recites a method of treating a T-cell mediated inflammation disorder in a subject having low activity or no activity of runt-related transcription 3 factor (RUNX3) gene product by delivering an active agent that induces expression or over-expression of RUNX3 to the immune cells of the subject, thereby inhibiting the proliferation of lymphocytes. Similarly, claim 13 recites a method for attenuating dendritic cell maturation in a subject having low activity or no activity of runt-

related transcription 3 factor (RUNX3) gene product by delivering an active agent that induces expression or over-expression of RUNX3 to the dendritic cells of the subject. Applicants contend that the claims as amended are enabled such that one of ordinary skill in the art would have known how to use the invention over the full scope of the claims as of the filing date of the instant application, without undue experimentation.

While the *Wands* factors are instructive in evaluating whether a claimed invention is enabled, no one factor is dispositive in determining if the enablement requirement has been met. *See Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 52 USPQ2d 1129, 1135-36 (Fed. Cir. 1999). Furthermore, while the specification must provide an enabling disclosure of the *invention*, it "need not teach (and preferably omits) information that is well-known to those of ordinary skill in the art." *See Spectra-Physics, Inc. v. Coherent, Inc.*, 887 F.2d 1524, 1534 (Fed. Cir. 1987). Additionally, "[n]ot every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be. United States specifications have often been criticized as too cluttered with details to give an easy understanding of what the invention really is." *See In re Gay*, 309 F.2d 769, 744; 134 USPQ 311, 316 (CCPA 1962). Finally, "an inventor need not explain every detail since he is speaking to those skilled in the art; what is conventional knowledge is read into the disclosure." *See In re Howarth*, 654 F.2d 105; 210 USPQ 689, 692 (CCPA 1981). Applicants remind the Examiner that the enablement requirement is dynamic – *i.e.*, as technology develops, what was once considered new becomes well within the understanding and capabilities of a person of ordinary skill in the art.

Where "the specification contains within it a connotation of how to use and/or the art recognizes that standard modes of administration are known and contemplated," the "how to

use" requirement of § 112, first paragraph, is satisfied. *See* M.P.E.P. § 2164.01(c), emphasis added). That section further states that ". . . it is not necessary to specify dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation." For example, if one skilled in the art would be able to discern an appropriate dosage or method of use without undue experimentation based on knowledge of compounds having similar physiological or biological activity to those claimed, then 35 U.S.C. 112, first paragraph would be satisfied. Similarly, if one skilled in the art would be able to discern an appropriate method of use without undue experimentation based on knowledge of similar methods to those claimed, then the enablement requirement would also be satisfied.

The instant specification contains much more than the required "connotation" of how to use the claimed invention. Contrary to the Examiner's assertions, Applicants submit that the specification provides a sufficient degree of guidance regarding how to perform the claimed methods, such that one of ordinary skill in the art would be able to routinely perform the methods as claimed without undue experimentation. For instance, the specification clearly shows that deficiency in RUNX3 as demonstrated in RUNX3 knock-out mice, causes asthma like symptoms (heavy breathing, accelerated heart rate, eosinophilic infiltration etc.). These mice were shown to develop a perturbed distribution of CD4+/CD8+ T lymphocytes (increased CD4+ and decreased CD8+) in the thymus, spleen and peripheral blood T cells. The mice also demonstrate increased levels of IL-5 in the bronchoalveolar lavage fluid. In addition, it was shown that RUNX3 expression is up-regulated during dendritic cell maturation.

Importantly, Applicants' specification has presented a human study conducted on asthma patients further demonstrating that particular SNPs in the RUNX3 gene were found to correlate

with asthma in humans. Supplementation of RUNX3 (via gene therapy) would, therefore, clearly be advantageous in cases of RUNX3 deficiency or defective RUNX3 gene.

Thus, Applicants have established the nexus between RUNX3 expression and T-cell mediated inflammation disorders, and contend that one of skill in the art at the time of invention would have accepted the disclosed models as reasonably correlating to the conditions associated with a deletion or disruption of RUNX3 and as reasonably predictive of the use of the peptide in a human gene therapy model for treating same. Contrary to the Examiner's contention (Office Action, page 7), a rigorous or an invariable, exact correlation is not required. *See* MPEP § 2164.02. Nor is a showing of efficacy the standard for determining enablement, as suggested by the Examiner (Office Action, at page 9). Such a standard would necessarily require that Applicants submit data from human clinical trials overseen by the FDA. However, it is improper for the Patent Office to request evidence regarding the degree of effectiveness of a compound in humans.

Whereas here Applicants have demonstrated that deletion or disruption of RUNX3 leads to enhanced maturation of dendritic cells (which are powerful stimulators of T-cell proliferation), known to play a significant role in the immune response and capable of eliciting proinflammatory responses, one of skill in the art (as of the filing date of the instant application) would have had a reasonable expectation that supplementing the deleted or disrupted gene product via a gene delivery system would produce the opposite effect of the knock-out condition (*e.g.*, reversing an associated inflammation disorder).

Further, the specification and rebuttal evidence provided herewith demonstrate that the ordinarily skilled artisan could discern an appropriate method of use without undue experimentation. As evidenced by the following publications (courtesy copies of which are

included herewith for the Examiner's convenience), prior to the filing date of the instant application, the art was replete with teachings for preparing gene delivery systems and administering same with a reasonable expectation of success in transferring genetic information to treat an inherited or acquired disorder:

- Albelda et al., Annals of Internal Medicine, 132(8):649-660 (2000) (providing an overview of vectors useful in gene therapy and concluding that while gene therapy is in its infancy, genes have been safely and successfully transferred into animals and patients);
- Anton et al., IDrugs, 3(3):251-256 (2000) (discussing developments in viral and nonviral vectors and use of such vectors for treating a variety of disorders (inheritable or acquired));
- Kay et al., Nature Genetics, 24:257-261 (2000) (evidencing gene transfer and expression of factor IX in haemophilia B patients treated with an AAV vector);
- Verma, Molecular Therapy, 1(6):493 (2000) (highlighting the success of gene therapy in treating infants suffering from SCID, and noting that although "a single sparrow does not make spring," the general condemnation of the field and unprecedented barrage of bad publicity was undeserved);
- Wang et al., Molecular Therapy, 1(2):154-158 (2000) (reporting on the sustained expression of therapeutic level of Factor IX in hemophilia B dogs by AAV-mediated gene therapy) (*see also* related study pertaining to mice Wang et al., Proc. Natl. Acad. Sci. USA, 96:3906-3910 (1999);

- del Pozo et al., Am J Respir Crit Care Med, 166:732-737 (2002) (reporting that gene therapy with galectin-3 inhibits an asthmatic reaction in a rat model having increased eosinophils and T cells in bronchoalveolar fluid and impaired pulmonary function);
- Manno, Seminars in Hematology, 40(Suppl 3):23-28 (July 2003) (reviewing the results of recent clinical studies investigating gene-based approaches to hemophilia treatment involving retroviral, adenoviral, and AAV vectors, as well as nonviral electroporation); and
- Russell et al., Mayo Clin Proc., 78:1370-1383 (Nov. 2003) (providing a primer on gene therapy and review of available vector systems, and noting that although hurdles to gene therapy remain, since 1989 (when the first human gene transfer experiment was performed), more than 600 human gene therapy protocols have been approved and more than 3000 patients have received gene therapy).

Accordingly, as of the date of invention of the instant application, production and use of gene delivery systems (*e.g.*, viral or non-viral gene transfer vectors used for transduction and expression) was well within the capability of those ordinarily skilled in the art to the degree that it would only require routine experimentation in order to produce a working vector and consequently administer it to a subject in need thereof. While no gene therapy products have been approved for sale yet, Applicants submit that it is undeniable that at the time of filing, the therapeutic use of gene therapy to treat inherited and/or acquired disorders was a well accepted model by those of ordinary skill in the art, as well as by the FDA, which has been actively involved in overseeing clinical investigations using such technologies since at least 2000.

Moreover, the Examiner's reliance on Zhou et al. (2004); O'Neil et al. (2004); Wallet et al. (2005); Green et al. (2007); Lambrecht et al. (2007); and Walsh et al. (2005) to show lack of enablement is unfounded. Determination of the enablement requirement is judged as of the filing date of the application. In the instant case, the filing date is December 30, 2003. However, all of the above references cited and relied on by the Examiner were published after the effective filing date of the instant application. Therefore, as a matter of law, these references cannot be used as evidence to show lack of enablement of the claimed invention. *See In re Hogan*, 559 F.2d 595, 604 (C.C.P.A. 1977) (holding later existing state of art which came into existence after filing date of application could not be considered in determining whether the application sufficiently complied with the enablement requirement). Although the Examiner's reliance on Kidd (Aug. 2003) is not improper, neither is it a persuasive basis for which to maintain the current enablement rejection in view of the publications provided by Applicants herewith supporting enablement of the claimed invention over its entire scope.

Here, the consideration of the *Wands* factors and the evidence as a whole favor enablement of the claimed invention. A plain reading of the instant specification shows that:

1. the Runx3 peptide was known to those of ordinary skill in the art at the time of filing and was therefore available as of the date of invention (*see, e.g.*, IDS reference BA);
2. the RUNX3 knock-out mice are useful as an animal model for T cell-mediated disorders and shows how to prepare same for use in methods that correlate to the claimed invention (*see, e.g.*, specification at paragraph [0120], Examples, and corresponding Figures);

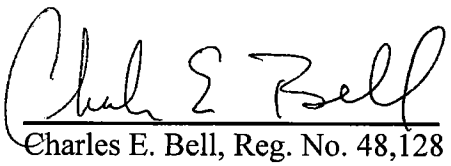
3. that RUNX3 is genetically associated with the T-cell mediated inflammation disorder, asthma, in humans (*see* Example 10); and
4. it contains a connotation of how to use the claimed invention and/or the art recognizes that standard modes of administration are known and contemplated (*i.e.*, one skilled in the art at the time of invention would have been able to discern an appropriate method of use without undue experimentation based on knowledge of similar methods to those claimed, as highlighted by the publications submitted herewith).

For all of the foregoing reasons, Applicants respectfully submit that claims 1-9 and 13 as amended herein are in condition for allowance. Reconsideration and withdrawal of the enablement rejection is respectfully requested. Should any questions or issues arise concerning the application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

With a two-month petition for extension of time and payment of the corresponding fee, this response is due on or before September 9, 2007. The Commissioner is hereby authorized to charge payment of any additional fees that may be required, or credit any overpayment of same, to Deposit Account No. 08-1935, Reference No. 2488.017.

Respectfully submitted,

Dated: September 6, 2007



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